

REMARKS

A. BACKGROUND

The present Amendment is in response to the Office Action mailed 26 September 2011. Claims 1, 2, 7, and 14 were pending and rejected in view of cited art. By this paper, no claims were amended, newly added, or canceled. Accordingly, claims 1, 2, 7, and 14 are currently pending.

B. CLAIM REJECTION UNDER 35 U.S.C. § 103

The Office Action rejects claims 1, 2, 7 and 14 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Pat. No. 6,358,918 ("*Schlag*") or Hallström et al (*Circulation*, 105, 3032-3038 (2002)) ("*Hallström*") in view of U.S. Pat. Pub. No. 20020136763 ("*Demopoulos*") and/or U.S. Pat. No. 6,525,017 ("*Lipton*"). Applicants respectfully traverse this rejection because, as will be shown below, the Office Action fails to consider the claimed invention as a whole and employs impermissible hindsight in making the rejection. In addition, Applicants respectfully traverse this rejection because *Schlag*, *Hallström*, *Demopoulos*, and *Lipton*, either alone or in combination, fail to teach or suggest the combination of elements recited in claims 1, 2, 7 and 14 and there is no reason for a person having ordinary skill in the art to modify the cited references in order to yield the claimed invention. The Office Action therefore fails to state a *prima facie* case of obviousness relative to the pending claims. In addition, or in the alternative, claims 1, 2, 7 and 14 are not obvious in view of the combination of *Schlag*, *Hallström*, *Demopoulos*, and *Lipton* because the claims define an invention that provides surprising and unexpected results relative to the teachings of the cited references, either alone or in combination, which objectively rebuts *prima facie* obviousness to the extent a case has been made, a point which Applicants do not concede.

I. THE OFFICE ACTION FAILS TO CONSIDER CLAIMED INVENTION AS A WHOLE AND MAKES IMPERMISSIBLE USE OF HINDSIGHT

Applicant respectfully traverses the rejections under §103 for the reason that the Examiner's analysis fails to consider the claimed invention as a whole. In addition, Applicant

respectfully traverses the rejections under §103 for the additional reason that the Examiner's analysis makes use of hindsight, which is impermissible.

According to MPEP §2141.02(I), "[i]n determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious." Likewise, the Court of Appeals for the Federal Circuit has stated that

[i]n making the assessment of differences, section 103 specifically requires consideration of the claimed invention "as a whole." Inventions typically are new combinations of existing principles or features. *Envtl. Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 698 (Fed.Cir.1983) (noting that "virtually all [inventions] are combinations of old elements."). The "as a whole" instruction in title 35 prevents evaluation of the invention part by part. Without this important requirement, an obviousness assessment might break an invention into its component parts (A + B + C), then find a prior art reference containing A, another containing B, and another containing C, and on that basis alone declare the invention obvious. This form of hindsight reasoning, using the invention as a roadmap to find its prior art components, would discount the value of combining various existing features or principles in a new way to achieve a new result; often the very definition of invention.

Section 103 precludes this hindsight discounting of the value of new combinations by requiring assessment of the invention as a whole. This court has provided further assurance of an "as a whole" assessment of the invention under § 103 by requiring a showing that an artisan of ordinary skill in the art at the time of invention, confronted by the same problems as the inventor and with no knowledge of the claimed invention, would select the various elements from the prior art and combine them in the claimed manner.

Ruiz v. A.B. Chance Co., 357 F.3d 1270, 1275 (Fed. Cir. 2004) (emphasis added).

The claims in the present case are directed to a "method for the treatment of ischemia" that includes administering a combination of "S-nitroso albumin ... and reduced glutathione." However, in formulating the rejection, the Examiner relies on a separate reference for essentially each element of the claims. For example, *Schlag* is relied upon for teaching treatment of ischemia with a nitrosated protein (e.g., S-nitroso albumin), *Hallström* is also relied upon for teaching treatment of ischemia with a nitrosated protein (e.g., S-nitroso human serum albumin), *Demopoulos* is relied upon for teaching administration of glutathione, optionally in combination

with "other therapeutic agents," for treating free radical-associated disorders, and *Lipton* is relied upon for teaching treating ischemic patients with a pharmaceutical composition comprising GSH. However, Applicant respectfully submits that there is no apparent connection between the disparate teachings of the references and the properties that they are alleged to teach, either alone or when combined. For instance, while the cited references may discuss the properties of S-nitroso albumin and GSH separately, there is no discussion, teaching, or suggestion of their co-administration and the properties or advantages that would be achieved by such a combination. The piecemeal approach taken in the Office Action is highly indicative of impermissible hindsight reconstruction, using the present invention as a template to pick and choose from among different elements from disparate prior art references.

This type of piecemeal reconstruction of the claimed invention is highly similar to the situation envisioned by the court in *Ruiz* where the Examiner "might break an invention into its component parts (A + B + C), then find a prior art reference containing A, another containing B, and another containing C, and on that basis alone declare the invention obvious." The court in *Ruiz* held this to be clearly improper. That is, allowing the Examiner to evaluate obviousness in a "part by part" fashion, such as has been done in the present case, is improper because it would preclude almost all patentability because, as acknowledged by the court in *Ruiz*, many if not almost all patentable "[i]nventions . . . are new combinations of existing principles or features." For this reason, Applicant respectfully requests the withdrawal of the rejection and immediate allowance of the claims. Accordingly, because claims 1, 2, 7, and 14, when considered as a whole, are not obvious, Applicants respectfully request that Examiner withdraw the rejection of claims 1, 2, 7, and 14 under 35 U.S.C. §103(a).

Moreover, in addition to failing to consider the claims as a whole, Applicant respectfully submits that each of the references cited by the Examiner require significant modification in order to yield the teachings that the Examiner has applied to the pending claims, and Applicant respectfully submits that the only conceivable motivation in the record for such modification are the teachings in Applicants' own disclosure, which is indicative of hindsight reconstruction.

With reference to *Schlag* and *Hallström*, it is acknowledged in the Office Action that they do not "teach combination of the S-NO-albumin with reduced glutathione (GSH)." Office Action, pg. 4. *Demopoulos* and *Lipton* allegedly overcome the acknowledged defects of *Schlag* and *Hallström*. With reference to *Demopoulos*, the Office Action alleges that the reference

teaches administration of glutathione alone or in combination with "other therapeutic agents" for treatment of free radical-associated disorders. Nevertheless, while *Demopoulos* may recite a laundry list of "other therapeutic agents" that glutathione may be combined with (see, e.g., ¶¶ [0131], [0134], [0136], [0139], [0141], [0144], [0148], [0149], [0155], [0156], or [0163]), Applicant submits that *Demopoulos* in no way suggests combination of glutathione with S-NO-albumin. Taken as a whole, Applicants respectfully submit that *Demopoulos*' extensive listing of compounds that glutathione may be combined with, which notably fails to include S-NO-albumin, teaches away from the claimed combination rather than toward it.

With reference to *Lipton*, the Office Action alleges that *Lipton* teaches treating ischemic patients with a pharmaceutical composition "comprising" GSH. Nevertheless, Applicants respectfully submit that in no instance does *Lipton* suggest any specific compound that may be included in such a pharmaceutical composition other than reduced glutathione or oxidized glutathione.

As such, Applicant respectfully submits that the only basis for selecting the specific combination of "S-nitroso albumin ... and reduced glutathione" from amongst the very different and wide ranging teachings of the cited art is Applicants' own disclosure. And while the art of record may teach that S-nitroso albumin and reduced glutathione are effective when administered separately, Applicants respectfully submit that the art of record is silent as to any reason for co-administering the combination of S-nitroso albumin and reduced glutathione for treatment of ischemia.

Moreover, the art of record is silent as to the synergistic and dose-dependent benefits that may be achieved by co-administration of S-nitroso albumin and reduced glutathione. See, e.g., Examples 1-3 of the present Application. As such, Applicant respectfully submits Applicants' own disclosure provides the only basis for picking amongst the disparate teachings of *Schlag*, *Hallström*, *Demopoulos*, and *Lipton* in order to yield a "method for the treatment of ischemia" that includes co-administering "S-nitroso albumin ... and reduced glutathione."

In addition to the above, Applicants respectfully note that when confronted with the reason for selecting a pharmaceutical for ischemia treatment, the question that the Examiner has to ask is as follows: "How would a skilled person try to get information regarding pharmaceuticals for ischemia treatment?" A Google internet search for the term "ischemia"

returns ~10.4 million documents. Likewise, a search of the USPTO for applications referring to ischemia returns ~23,400 patents and ~35,000 patent applications.

Confronted with that number of potential prior art references, how would a person having ordinary skill in the art choose from all the large number of potential sources information and choose just the four different references cited by the examiner without hindsight with respect to the present invention and/or without the use of keyword searching using terms from Applicant's claims and disclosure? Clearly there are thousands and thousands of other and different possibilities remaining. The Supreme Court in *KSR v. Teleflex* is quite clear that a specific combination that is not taught or suggested by the art may nevertheless be "obvious to try" where there is a "finite number" (*i.e.*, reasonably small) of possible combinations and a known reason to combine the claimed components. Here, neither prong of this test is present, which is further evidence of the patentability of the claimed invention.

Accordingly, because the Office Action has objectively employed impermissible hindsight in rejecting claims 1, 2, 7 and 14, Applicant respectfully requests that Examiner withdraw the rejection of claims 1, 2, 7 and 14 under 35 U.S.C. §103(a).

II. THE CITED REFERENCES FAIL TO TEACH OR SUGGEST EACH AND EVERY ELEMENT OF THE PENDING CLAIMS

The foregoing notwithstanding, Applicant respectfully submits that the Office Action has not established a *prima facie* case of obviousness because the cited references fail to teach or suggest each and every element of the pending claims. A detailed explanation why the present invention is unobvious in view of both references, including a combination thereof, was already provided. The fact that prosecution was reopened following the Pre-Appeal Brief Conference and Panel Review stands as proof that the present claims cannot be held as obvious over the previous rejection, which was the combination of *Schlag* and *Hallström*. It is noted that the Examiner now relies upon *Lipton* and *Demopououlos* in addition to *Schlag* and *Hallström* to allege *prima facie* obviousness of the claimed invention.

Nevertheless, Applicant respectfully submits that the present Office Action has largely recycled the rejected arguments from the previous Office Action with respect to *Schlag* and *Hallström* and adds *Demopououlos* and *Lipton* to allegedly provide the missing teachings with respect to co-administration of reduced glutathione and S-NO-albumin that the Examiner

previously alleged were to be found in the teachings of *Schlag* and *Hallström*. Nonetheless, Applicant respectfully submits that the combination of *Schlag*, *Hallström*, *Demopoulos* and *Lipton* goes no further than *Schlag* and *Hallström* in teaching or suggesting the combination of elements in the pending claims. Moreover, Applicant submits that there is no reason for a person having ordinary skill in the art to modify the cited references in order to yield the claimed invention. As a result, the Office Action therefore fails to state a *prima facie* case of obviousness relative to the pending claims.

Claim 1 is directed to a method for the treatment of ischemia. The method of claim 1 comprises administering a pharmaceutical preparation to a subject in need thereof comprising a therapeutic protein having nitrosated SH-groups, wherein the therapeutic protein is S-nitroso albumin and "reduced glutathione." Thus, claim 1 requires administering both S-nitroso albumin and reduced glutathione to a subject to treat ischemia.

In rejecting the claims over *Schlag*, *Hallström*, *Demopoulos* and *Lipton*, the Office Action initially interprets the relevant teachings of *Schlag* as follows:

Schlag et al. teach a method of treating an ischemia (cerebral ischemia) comprising administering to a patient in need thereof a pharmaceutical composition comprising at least one (plurality) thiol group containing protein (claim 16), wherein at least 95% or 90% of the thiol groups of said protein are nitrosated, i.e., S-nitrosated protein (claims 19 and 20), and wherein said 'at least one thiol group containing protein' that has been nitrosated is S-nitroso-albumin (claim 21), as applied to claim 1.

Office Action, pp. 3 (emphasis in original).

According to the Office Action, *Hallström* teaches "the use of S-nitrosated human serum albumin (S-NO-HAS) to treat ischemic condition." Office Action, pg. 3. The Office action acknowledges that "neither Schlag et al. nor Halstrom et al. expressly teach combination of the S-NO-albumin with the reduced glutathione (GSH) for treating ischemia." Office Action, pg. 4. And indeed this must be so in light of the outcome of the pre-appeal conference.

Demopoulos is relied upon in the Office Action for teaching that "glutathione can be used in combination with other therapies [e.g., "other therapeutic agents" of which there are hundreds, thousands or millions] for treating free radical-associated disorders." *Id.* *Lipton* is relied upon for teaching treating ischemic patients with "a pharmaceutical composition comprising GSH." *Id.*

The Office Action goes on to allege that it is obvious to combine the teachings of *Schlag*, *Hallström*, *Demopoulos*, and *Lipton* in order to yield the claimed combination. In particular, the Office Action alleges that *Schlag* teaches that it is "particularly preferred" to administer S-NO-albumin with "'any other proteins/polypeptides' containing free thiol groups." *Id.* The Office Action further alleges that *Demopoulos* teaches the "feasibility of combining glutathione with other 'therapeutic protein(s)/peptide(s)' for treating therapies" (Office Action, pg. 4) and that *Lipton* has demonstrated that reduced glutathione is "therapeutically active in treating ischemia" (Office Action, pg. 5).

In spite of what is alleged in the Office Action, Applicant respectfully submits that *Schlag*, *Hallström*, *Demopoulos*, and *Lipton*, either alone or in combination, fail to teach or suggest co-administration of reduced glutathione and S-NO-albumin. Even assuming for the sake of argument that *Demopoulos* and *Lipton* teach what the Examiner alleges, Applicant respectfully submits that these references fail to overcome the acknowledged deficiencies of *Schlag* and *Hallström*. Applicant respectfully submits that, at most, the only thing that the cited references show is that reduced glutathione and S-NO-albumin may be separately effective for treating ischemia. Applicant respectfully submits that it is not necessarily scientifically valid to say that if two therapeutic agents are good separately they must be better if used together. For instance, aspirin and ibuprofen are both effective for treating pain and inflammation, but dosages of each that are safe if taken separately can result in a toxic overdose if taken together. This point is driven home by *Demopoulos*. In paragraph [0127] is stated: "Because the glutathione and ascorbic acid are administered in relatively high doses, it is preferred that these components be highly purified, to eliminate impurities, toxins or other chemicals, which may destabilize the formulation or produce toxic effects or side effects." Based on this teaching in *Demopoulos*, Applicant respectfully submits that a person having ordinary skill in the art would not combine glutathione with S-NO-albumin because the combination "may destabilize the formulation or produce toxic effects or side effects." Moreover, it would take undue experimentation to determine whether the specific combination of reduced glutathione and S-NO-albumin is safe and effective if used together and, if so, in what proportions and/or amounts in order to avoid a toxic combination. This, of course, is finding the veritable "needle in a haystack".

With further reference to *Demopoulos*, while *Demopoulos* may recite a laundry list of "other therapeutic agents" that glutathione may be combined with (see, e.g., ¶¶ [0131], [0134],

[0136], [0139], [0141], [0144], [0148], [0149], [0155], [0156], or [0163]), Applicant submits that *Demopoulos* in no way suggests a combination of glutathione and S-NO-albumin among the thousands of possible combinations disclosed therein. This is doubtlessly significant. It would take undue experimentation to first work through the thousands of combinations disclosed in *Demopoulos*, none of which are the claimed combination, and then continuing to work through combinations not taught or suggested in *Demopoulos* until the claimed combination is found and validated. Taken as a whole, Applicant respectfully submits that *Demopoulos*' exhaustive listing of compounds that glutathione may be combined with, none of which is reduced glutathione, leads away from the claimed combination rather than toward it. With further reference to *Lipton*, the Office Action alleges that *Lipton* teaches treating ischemic patients with a pharmaceutical composition "comprising" glutathione. Nevertheless, Applicant cannot find, nor has the Examiner indicated any teaching of any specific compounds, that may be included in such a composition other than reduced glutathione or oxidized glutathione.

With reference to *Schlag* and *Hallström*, the only suggestion to be found in the record suggesting that reduced glutathione may be chosen from amongst the millions of possible proteins/polypeptides that contain free thiols for combination with S-NO-albumin is the Examiner's own suggestion that it "could" be reduced glutathione. *Id.* That sounds like "obvious to try" and, as noted above, this type of rejection only applies where there is a "finite number" of different possible combinations rather than thousands or millions as here. Applicant respectfully submits that the Examiner's own unsupported conjecture does not substitute for a legal finding of obviousness. Moreover, it was forcefully argued in the last response that *Schlag* actually teaches away from the combination of "S-nitroso albumin" and "reduced glutathione" when treating a human. Such arguments were accepted in the pre-appeal conference and resulted in reopening prosecution in view of the deficiency of the previous rejection.

According to *Schlag*,

An advantage of the nitrosated preparation according to the invention also consists in that on account of its high S-nitroso content it can be administered in smaller amounts than preparations having a substantially lower S-nitroso content. *What is also important is that the release of the active NO groups of the proteins used according to the invention takes place over a longer period of time, and, on the whole, the kinetics of this reaction is advantageous under physiological conditions.*

Col. 7, ln. 25-33 (emphasis added). According to *Schlag*, an "advantage" and "important" feature of the "nitrosated preparation according to the invention" is the "release of the active NO groups" is better than in other preparations because it "takes place over a longer period of time". Thus, *Schlag* teaches away from preparations in which "release of the active NO groups ... takes place over a [shorter] period of time" (*i.e.*, is accelerated as compared to the "nitrosated preparation according to the invention" of *Schlag*).

As a baseline comparison, *Schlag* therefore teaches away from "nitrosated preparations" in which "release of the active NO groups" is accelerated compared to "N-nitroso human serum albumin". Because the claimed invention includes a combination that has been shown to accelerate the release of NO compared to N-nitroso human serum albumin by itself (see, e.g., Example 1), while *Schlag* strongly advocates preparations that delay release of NO, *Schlag* teaches away from the claimed invention.

For these reasons, Applicant submits that the Office Action fails to state a *prima facie* case of obviousness relative to the claims presented herein. Accordingly, because the Office Action has objectively failed to state a *prima facie* case of obviousness relative to claims 1, 2, 7 and 14, Applicant respectfully requests that Examiner withdraw the rejection of claims 1, 2, 7 and 14 under 35 U.S.C. §103(a).

III. THE CLAIMS PROVIDE SURPRISING AND UNEXPECTED RESULTS RELATIVE TO THE TEACHINGS OF THE CITED ART.

In addition to the foregoing, Applicant again respectfully submits that the preparations defined in claims 1, 2, 7 and 14 provide surprising and unexpected results relative to the teachings of the cited art. Evidence that the compound or composition possesses superior and unexpected properties in one of a spectrum of common properties can be sufficient to rebut a *prima facie* case of obviousness. MPEP § 2145 (citing *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987)). As discussed and agreed to during the Examiner Interview of 26 April 2011, the showing of unexpected (*i.e.*, unpredictable) results could rebut *prima facie* obviousness. In particular, the Examiner's supervisor acknowledged that a showing of unexpected and unpredictable results of using the claimed combination compared to using S-nitroso human serum albumin by itself would be sufficient to overcome *prima facie* obviousness to the extent it exists.

Examples 1-3 of the Application (See Application ¶¶ [0062]-[0076]) describe several different types of synergistic effects that were observed when S-nitroso albumin was administered in combination with reduced glutathione. These results were explicitly compared to the administration of S-nitroso albumin alone. Moreover, Applicant respectfully submits that such synergistic effects are "greater than expected" (see, MPEP § 716.02(a)) and that they could not have been predicted by a person having ordinary skill in the art. Thus, the results shown in Examples 1-3 are surprising, unexpected and unpredictable, which are touchstones of patentability.

Example 1 demonstrates a drop in blood pressure when S-nitroso albumin was administered in combination with reduced glutathione as compared to administering S-nitroso albumin alone. Example 2 demonstrates an increase in NO release when S-nitroso albumin was administered in combination with reduced glutathione as compared to administering S-nitroso albumin alone. Example 3 demonstrates a drop in platelet aggregation when S-nitroso albumin was administered in combination with reduced glutathione as compared to administering S-nitroso albumin alone. In addition, such synergistic effects of administering S-nitroso albumin in combination with reduced glutathione occurred in a dose-dependent manner. Applicants respectfully submit that this dose-dependent effect is "greater than expected" and could not have been predicted based on what is disclosed in the art of record.

Examples 1-3 of the Application demonstrate the significant benefit of administering reduced glutathione (*i.e.*, apart from the glutathione that naturally exists in the subject) in combination with nitrosated albumin. Examples 1-3 are a direct comparison between the claimed invention and a technique similar to the one described in *Schlag* and *Hallström* (*i.e.*, administration of S-nitroso human serum albumin by itself), which are, by definition, the closest prior art since they are the primary and first secondary references cited in rejecting the claims. There is no teaching or suggestion in *Schlag*, *Hallström* or any other art of record from which the specific unexpected results shown in Examples 1-3 could be predicted.

Nor does the Office Action cite to any teaching or suggestion in the prior art that administering the combination of S-nitroso albumin and reduced glutathione would result in *any* of a drop in blood pressure (Example 1), an increase in NO release (Example 2), and a drop in platelet aggregation (Example 3), much less all three. Hence, even if it could be shown that the combination of *Schlag* and *Hallström* suggests the use of S-nitroso human serum albumin and

reduced glutathione to treat ischemia for the reasons set forth in the Office Action such that the claims are *prima facie* obvious, the showing of not one but three unexpected and unpredictable results is effective to rebut *prima facie* obviousness.

In short, the fact that administering reduced glutathione in combination with S-nitroso albumin provides surprising, unexpected and unpredictable results (*i.e.*, blood pressure drop, increase in NO release, and drop in platelet aggregation) that is "greater than expected" than administering S-nitroso human serum albumin by itself as taught in *Schlag* and *Hallström* is objective evidence that the claimed invention is unobvious over the combination of *Schlag* and *Hallström*.

In the present Office Action, the Examiner states that "in view of the . . . combined teachings of the references[,] a synergistic effect of GSH and the S-NO-Albumin . . . would be expected by one skilled in the art." Office Action, pg. 6. However, Applicant respectfully submits that this statement and other statements in the Office Action do not constitute a specific rebuttal of the evidence that has been presented showing that co-administration of reduced glutathione and S-NO-albumin provides a synergistic effect that is surprising and unexpected effect (*i.e.*, "greater than expected"). In other words, the Examiner's assertions are mere conjecture, unsupported by evidence in the record apart from Applicants' own Examples. Unless such a rebuttal is forthcoming, Applicant requests withdrawal of the rejection of claims 1, 2, 7 and 14 under 35 U.S.C. § 103(a).

For these reasons, Applicant submits that to the extent that the Office Action may state a *prima facie* case of obviousness relative to the claims presented herein (a point that Applicant does not concede), the surprising and unexpected results presented in the Application overcome such a *prima facie* case. Accordingly, because claims 1, 2, 7 and 14 provide surprising and unexpected results relative to the teachings of the cited art, Applicant respectfully requests that Examiner withdraw the rejection of claims 1, 2, 7 and 14 under 35 U.S.C. §103(a).

C. CONCLUSION

For at least the foregoing reasons, Applicant respectfully submits that the pending claims are unobvious by the art of record.

In the event the Examiner finds any remaining impediment to a prompt allowance of this application that may be clarified through a telephone interview or which may be overcome by Examiner amendment, the Examiner is requested to contact the undersigned attorney.

The Commissioner is hereby authorized to charge payment of any of the following fees that may be applicable to this communication, or credit any overpayment, to **Deposit Account No. 23-3178**: (1) any filing fees required under 37 CFR § 1.16; (2) any patent application and reexamination processing fees under 37 CFR § 1.17; and/or (3) any post issuance fees under 37 CFR § 1.20. In addition, if any additional extension of time is required, which has not otherwise been requested, please consider this a petition therefore and charge any additional fees that may be required to **Deposit Account No. 23-3178**.

Dated this 25th day of January 2012.

Respectfully submitted,

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